

(13)

On page 26, along the lefthand margin, delete "Glucoseinfusions-Rate (mg*kg⁻¹*min⁻¹)" and insert therefor --Glucose infusion rate (mg.kg⁻¹.min⁻¹)--.

On page 26, in the vertical space between the sets of graphs, delete "Blutglucose (mmol/l)" and insert therefor --Blood glucose (mmol/l)--.

On page 26, below the graphs and above "Key:", delete the two recitations of "Minuten" and insert therefor --Minutes--.

(KJ) On page 26, last seven lines, delete "Key:...Minutes".

Please insert the SEQUENCE LISTING contained in the attached sheets after page 26 and before page 27, i.e., before the claims.

IN THE CLAIMS:

Please cancel claims 37-40, and rewrite as, respectively, new claims 63-66.

Please cancel claim 59, and rewrite as new claim 67.

Please amend the claims as follows:

Page 27, line 1, delete "Patent claims" and insert therefor --We claim:--.

(W.J.) Claim 1, lines 7-11, after "acidic amino acid residue" delete ", it optionally being possible...B chain to be absent".

Claim 8, line 31, "one or more of claims 1 to 7" and insert therefor --claim 1--.

Claim 9, line 3, delete "one or more of claims 1 to 8" and insert therefor --claim 1--.

Claim 13, line 20, delete "one or more of claims 1 to 12" and insert therefor --claim 1--.

Claim 14, line 26, delete "one or more of claims 1 to 13" and insert therefor --claim 1--.

Claim 17, line 9, delete "one or more of claims 1 to 13" and insert therefor --claim 1--.

Claim 26, line 15, delete "one or more of claims 1 to 25" and insert therefor --claim 1--.

Claim 32, line 26, delete "one or more of claims 1 to 30" and insert therefor --claim 1--.

Claim 41, line 15, delete "claim 37" and insert therefor --claim 63--.

Claim 42, line 17, delete "claim 38" and insert therefor --claim 64--.

Claim 43, line 19, delete "claim 39" and insert therefor --claim 65--.

Claim 44, line 21, delete "claim 40" and insert therefor --claim 66--.

Claim 53, line 27, delete "one of claims 49 to 52" and insert therefor --claim 49--.

Claim 54, lines 30-31, delete "one or more of claims 1 to 30" and insert therefor
--claim 1--.

Claim 58, line 14, delete "one of claims 54 to 56" and insert therefor --claim 54--.

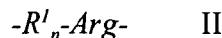
Please add the following new claims:

42
60. An insulin derivative or a physiologically tolerable salt thereof as claimed in
claim 1, wherein asparagine (Asn) in position 21 of the A chain is replaced by Asp, Gly, Ser, Thr
or Ala.

43
61. An insulin derivative or a physiologically tolerable salt thereof as claimed in
claim 1, wherein phenylalanine (Phe) in position B1 of the B chain is absent.

44
62. An insulin derivative or a physiologically tolerable salt thereof as claimed in
claim 1, wherein the amino acid residue in position B30 of the B chain is absent.

63. A process for the preparation of an insulin derivative as claimed in claim 26, comprising the construction of a replicable, expression vehicle which contains a DNA sequence which codes for a precursor of the insulin derivative, in which the amino acid residue in position A1 of the A chain is linked to the amino acid residue B30 of the B chain via a peptide chain of the formula II



in which R^1_n is a peptide chain having n amino acid residues and n is an integer from 0 to 34, and the B chain is prolonged in position B1 by a peptide chain of the formula III



in which R^2_m is a peptide chain having m amino acid residues, m is an integer from 0 to 40 and p is 0, 1 or 2, expression in a host cell and release of the insulin derivative from its precursor using chemical and/or enzymatic methods, wherein the precursor of the insulin derivative has the sequence

Met Ala Thr Thr Ser Thr Gly Asn Ser Ala Arg Phe Val Lys Gln

His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys

Gly Glu Arg Gly Phe Phe Tyr Thr Ile Lys Thr Arg Arg Glu Ala

Glu Asp Pro Gln Val Gly Gln Val Glu Leu Gly Gly Pro Gly

Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys

Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr

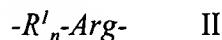
Gln Leu Glu Asn Tyr Cys Asp

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(SEQ ID No.: 11).

64. A process for the preparation of an insulin derivative as claimed in claim 28, comprising the construction of a replicable expression vehicle which contains a DNA sequence which codes for a precursor of the insulin derivative, in which the amino acid residue in position A1 of the A chain is linked to the amino acid residue B30 of the B chain via a peptide chain of the formula II



in which R'^n_1 is a peptide chain having n amino acid residues and n is an integer from 0 to 34, and the B chain is prolonged in position B1 by a peptide chain of the formula III



in which R^2_m is a peptide chain having m amino acid residues, m is an integer from 0 to 40 and p is 0, 1 or 2, expression in a host cell and release of the insulin derivative from its precursor using chemical and/or enzymatic methods, wherein the precursor of the insulin derivative has the sequence

Met Ala Thr Thr Ser Thr Gly Asn Ser Ala Arg

Phe Val Lys Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu

Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Glu Thr

Arg Arg Glu Ala Glu Asp Pro Gln Val Gly Gln Val Glu Leu Gly

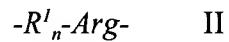
Gly Gly Pro Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly

Ser Leu Gln Lys Arg

Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln
Leu Glu Asn Tyr Cys Asn

(SEQ ID NO.: 6).

65. A process for the preparation of an insulin derivative as claimed in claim 30, comprising the construction of a replicable expression vehicle which contains a DNA sequence which codes for a precursor of the insulin derivative, in which the amino acid residue in position A1 of the A chain is linked to the amino acid residue B30 of the B chain via a peptide chain of the formula II



in which R^1_n is a peptide chain having n amino acid residues and n is an integer from 0 to 34, and the B chain is prolonged in position B1 by a peptide chain of the formula III



in which R^2_m is a peptide chain having m amino acid residues, m is an integer from 0 to 40 and p is 0, 1 or 2, expression in a host cell and release of the insulin derivative from its precursor using chemical and/or enzymatic methods, wherein the precursor of the insulin derivative has the sequence

Met Ala Thr Thr Ser Thr Gly Asn Ser Ala Arg
Phe Val Lys Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu
Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Ile Pro Lys Thr

Arg Arg Glu Ala Glu Asp Pro Gln Val Gly Gln Val Glu Leu Gly
Gly Gly Pro Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly
Ser Leu Gln Lys Arg
Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln
Leu Glu Asn Tyr Cys Asn

(SEQ ID NO.: 8).

66. A process for the preparation of an insulin derivative as claimed in claim 31, comprising the construction of a replicable expression vehicle which contains a DNA sequence which codes for a precursor of the insulin derivative, in which the amino acid residue in position A1 of the A chain is linked to the amino acid residue B30 of the B chain via a peptide chain of the formula II

$-R^1_n\text{-}Arg-$ II

in which R^1_n is a peptide chain having n amino acid residues and n is an integer from 0 to 34, and the B chain is prolonged in position B1 by a peptide chain of the formula III

$Met\text{-}R^2_m\text{-}(Arg)_p\text{-}$ III

in which R^2_m is a peptide chain having m amino acid residues, m is an integer from 0 to 40 and p is 0, 1 or 2, expression in a host cell and release of the insulin derivative from its precursor using chemical and/or enzymatic methods, wherein the precursor of the insulin derivative has the sequence

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